### 10.7.5.2 Laboratory Animal Estimates

Tables 10-26 through 10-31 provide the deposition fractions of various particle sizes (MMAD) for either a relatively monodisperse ($\sigma_g$ = 1.3) versus a more polydisperse ($\sigma_g$ = 2.4) distribution in humans or rats. Deposition fractions of these aerosols for an adult male human normal augmenter and mouth breather with a general population activity pattern were calculated using the ICRP66 model (ICRP66, 1994). The deposition fraction for each respiratory tract region is presented: ET in Tables 10-26 and 10-27; TB in Tables 10-28 and 10-29; and A in Tables 10-30 and 10-31. These regional deposition fractions are shown plotted in Figure 10-54. The left side in each panel represents the deposition fractions for the relatively monodisperse aerosol ($\sigma_g$ = 1.3) and the right side in each panel represents the more polydisperse aerosol ($\sigma_g$ = 2.4). Note that the y-axis scale changes from one panel to the other and from panel to panel. As discussed in Section 10.5, polydispersity in the aerodynamic particle size range tends to smear the regional deposition across the range of particles. The interspecies differences in fractional deposition are readily apparent from these figures.

In the TB region, Figure 10-54 illustrates that at the smaller particle diameters (MMAD < 2 $\mu$m for $\sigma_g$ = 1.3) the rats have higher deposition fractions than normal augmenter (nasal breathing) humans. At larger particle diameters (MMAD > 2.5 $\mu$m for $\sigma_g$ = 1.3), rats have very little deposition in the TB or A regions due to the low inhalability of these particles. This may help explain why inhalation exposures of rodents to high concentrations of larger particles have exhibited little effect in some bioassays.

The information in Tables 10-26 through 10-31 and depicted in the panels of Figure 10-54 can be used to calculate the deposition fraction term in Equations 10-50 and 10-54. The average ventilation rates and parameters such as surface area which could be used for normalizing factors for laboratory animals are found in Appendix 10B, Table 10B-2.

**TABLE 10-26. EXTRATHORACIC DEPOSITION FRACTIONS OF INHALED MONODISPERSE AEROSOLS ($\sigma_g$=1.3) IN RATS AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"**

| MMAD | Normal Augmenter | Mouth Breather | Rat |
|---|---|---|---|
| 1 | 0.273 | 0.074 | 0.18 |
| 1.5 | 0.443 | 0.141 | 0.55 |
| 2 | 0.566 | 0.209 | 0.74 |
| 2.5 | 0.651 | 0.270 | 0.77 |
| 3 | 0.711 | 0.326 | 0.76 |
| 3.5 | 0.754 | 0.375 | 0.73 |
| 4 | 0.785 | 0.420 | 0.70 |

**TABLE 10-27. EXTRATHORACIC DEPOSITION FRACTIONS OF INHALED POLYDISPERSE AEROSOLS ($\sigma_g$=2.4) IN RATS AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"**

| MMAD | Normal Augmenter | Mouth Breather | Rat |
|---|---|---|---|
| 1 | 0.326 | 0.126 | 0.30 |
| 1.5 | 0.442 | 0.193 | 0.42 |
| 2 | 0.524 | 0.250 | 0.49 |
| 2.5 | 0.582 | 0.299 | 0.53 |
| 3 | 0.624 | 0.340 | 0.55 |
| 3.5 | 0.655 | 0.374 | 0.56 |
| 4 | 0.678 | 0.404 | 0.56 |

**TABLE 10-28. TRACHEOBRONCHIAL DEPOSITION FRACTIONS OF INHALED MONODISPERSE AEROSOLS ($\sigma_g$=1.3) IN RATS AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"**

| MMAD | Normal Augmenter | Mouth Breather | Rat |
|---|---|---|---|
| 1 | 0.022 | 0.026 | 0.10 |
| 1.5 | 0.033 | 0.048 | 0.06 |
| 2 | 0.042 | 0.074 | 0.03 |
| 2.5 | 0.048 | 0.101 | 0.01 |
| 3 | 0.050 | 0.125 | 0.005 |
| 3.5 | 0.050 | 0.144 | 0.002 |
| 4 | 0.049 | 0.159 | 0.001 |

**TABLE 10-29. TRACHEOBRONCHIAL DEPOSITION FRACTIONS OF INHALED POLYDISPERSE AEROSOLS ($\sigma_g$=2.4) IN RATS AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"**

| MMAD | Normal Augmenter | Mouth Breather | Rat |
|---|---|---|---|
| 1 | 0.028 | 0.049 | 0.06 |
| 1.5 | 0.032 | 0.068 | 0.05 |
| 2 | 0.035 | 0.084 | 0.04 |
| 2.5 | 0.036 | 0.096 | 0.031 |
| 3 | 0.036 | 0.104 | 0.025 |
| 3.5 | 0.036 | 0.110 | 0.021 |
| 4 | 0.035 | 0.114 | 0.017 |

**TABLE 10-30. ALVEOLAR DEPOSITION FRACTIONS OF INHALED MONODISPERSE AEROSOLS ($\sigma_g$=1.3) IN RATS AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"**

| MMAD | Normal Augmenter | Mouth Breather | Rat |
|---|---|---|---|
| 1 | 0.119 | 0.140 | 0.06 |
| 1.5 | 0.146 | 0.120 | 0.10 |
| 2 | 0.150 | 0.237 | 0.06 |
| 2.5 | 0.142 | 0.256 | 0.02 |
| 3 | 0.126 | 0.258 | 0.011 |
| 3.5 | 0.109 | 0.248 | 0.005 |
| 4 | 0.092 | 0.230 | 0.002 |

**TABLE 10-31. ALVEOLAR DEPOSITION FRACTIONS OF INHALED POLYDISPERSE AEROSOLS ($\sigma_g$=2.4) IN RATS AND HUMAN "NORMAL AUGMENTER" AND "MOUTH BREATHER"**

| MMAD | Normal Augmenter | Mouth Breather | Rat |
|---|---|---|---|
| 1 | 0.111 | 0.151 | 0.04 |
| 1.5 | 0.112 | 0.171 | 0.04 |
| 2 | 0.109 | 0.180 | 0.035 |
| 2.5 | 0.103 | 0.179 | 0.031 |
| 3 | 0.096 | 0.175 | 0.027 |
| 3.5 | 0.089 | 0.169 | 0.023 |
| 4 | 0.082 | 0.161 | 0.020 |

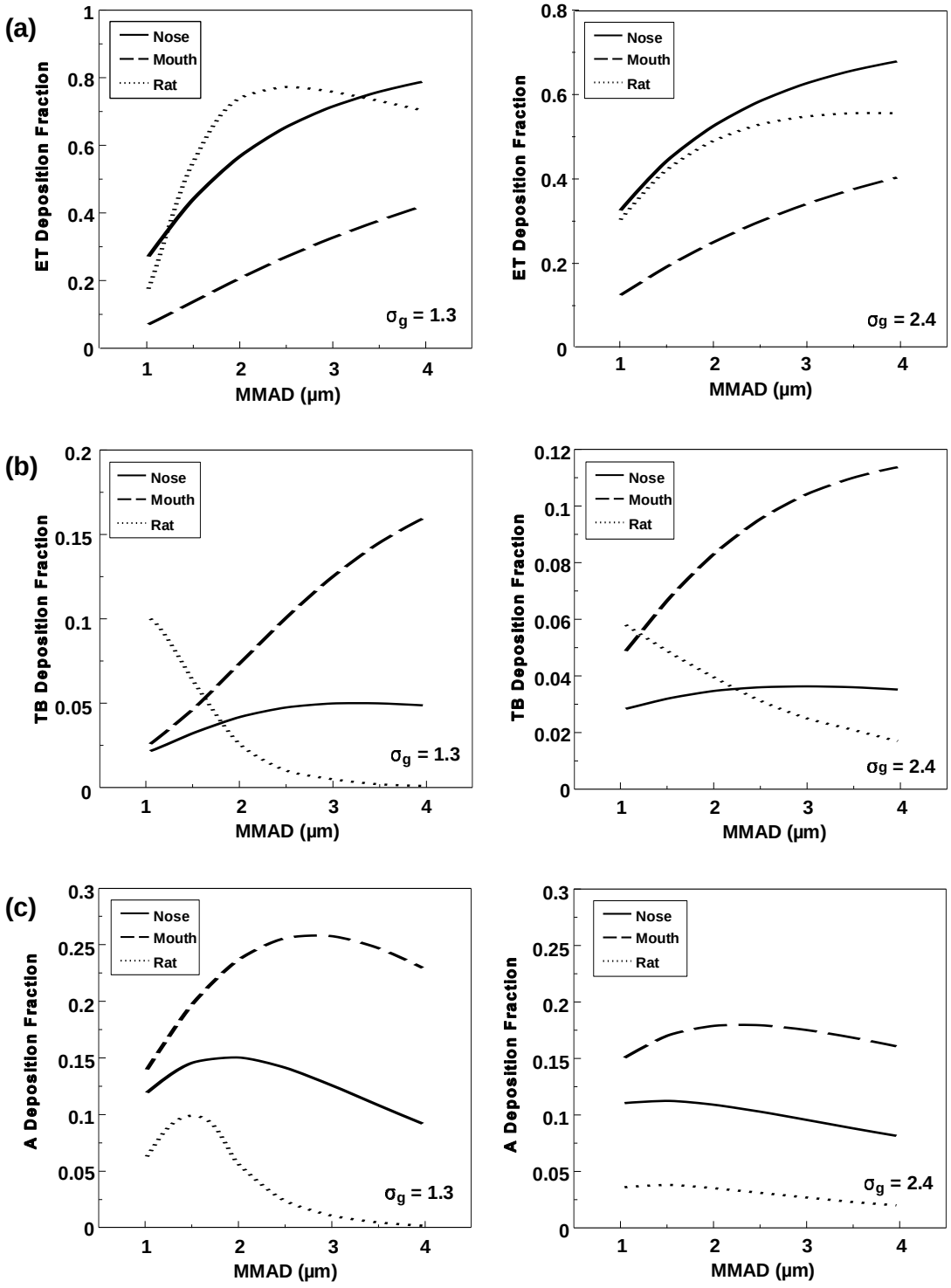


**Figure 10-54. Predicted extrathoracic deposition fractions versus mass median aerodynamic diameter (MMAD) of inhaled monodisperse ($\sigma_g$ = 1.3) aerosols shown in left-side panels or polydisperse ($\sigma_g$ = 2.4) aerosols shown in right-side panels for humans (nose versus mouth breathing) and rats (obligatory nose breathers), for (a) the extrathoracic region, (b) tracheobronchial region, and (c) alveolar region.**

Respiratory tract region surface areas for humans are found in Table 10B-1. The human male adult general population activity pattern in Table 10B-1 corresponds to a daily ventilation volume of 19.9 $m^3$/day. This is the average ventilation rate that was used to run the LUDEP® simulations and would be used in the denominator of Equations 10-51 or 10-55. The normal augmenter or mouth breather deposition fractions found in Tables 10-26 through 10-31 represents the sum of the $Fr_H$ factors in the denominator of the expression found in Equations 10-51 and 10-55. Likewise, the deposition fractions for the rat represent the $Fr_A$ factor in Equations 10-53 and 10-57.

Because particles initially deposit along the surface of the respiratory tract, regional surface area is chosen as the normalizing factor for calculation of the regional deposited dose ratio (RDDR), as described in Equation 10-50, in order to characterize "acute" effects. Assuming an exposure to an aerosol with a MMAD of 1.0 $\mu$m and $\sigma_g$ = 1.3, Equation 10-51 can be used to calculate $RDDR_{A[ACT]}$ estimates using the deposition fractions provided in Tables 10-26 through 10-31 and surface area and ventilation rate parameters provided in Tables 10B-1 and 10B-2 in Appendix 10B. A $RDDR_{A[ACT]}$ value of 1.54 is calculated for rats using the alveolar surface area as a normalizing factor. The $RDDR_{A[ACT]}$ value for each species would be applied to an experimental exposure concentration from a laboratory toxicology study using rats to calculate a human equivalent concentration.

Interspecies extrapolation to HEC values allows for comparison among species. For example, if a rat exhibited an effect in the alveolar region when exposed to an aerosol with a MMAD = 1.0 $\mu$m and $\sigma_g$ = 1.3 at an exposure concentration of 100 $\mu g/m^3$, the resultant HEC value calculated for the rat would be 154 $\mu g/m^3$. This HEC would result in a similar alveolar deposited dose and thereby a similar effect in humans, assuming species sensitivity to a given dose is equal. Although laboratory species may be exposed to the same aerosol at the same concentration, each would have a different fractional deposition, which when normalized to regional surface area, could result in different HEC estimates. Thus, taking into account species differences in dosimetry is necessary before comparing effective concentrations when interpreting toxicity data.

For tracheobronchial effects, the $RDDR_{TB[ACT]}$ would be used to adjust exposure concentrations for interspecies differences in dosimetry. For an aerosol with an MMAD = 1.0 $\mu$m and $\sigma_g$ = 1.3, the $RDDR_{TB[ACT]}$ value is 9.95 for rats. For an aerosol with an MMAD = 2.5

and $\sigma_g$ = 2.4, the $RDDR_{TB[ACT]}$ value is 1.89. The decrease in the value is due to the decreased inhalability of the larger particle diameter and the effect of polydispersity. Similarly, the $RDDR_{A[ACT]}$ value for an aerosol with an MMAD = 2.5 $\mu$m and $\sigma_g$ = 2.4 is 0.88 for rats, whereas it was 1.54 for the more monodisperse aerosol.

## 10.7.6 Retained Dose Estimates

An important issue in inhalation toxicology is the relationship between repeated or chronic inhalation exposures and the resulting alveolar burdens of exposure material achieved in the human lung versus the lungs of laboratory animal species. It is generally assumed that the magnitude of the alveolar burden of particles produced during an inhalation exposure is an important determinant of biological responses to the inhaled particles. Therefore, understanding the basis for differences among species in alveolar burdens that will result from well-defined inhalation exposures will provide investigators with a better understanding of alveolar burdens that would result from exposures of various mammalian species to the same aerosol. Alternatively, the exposure conditions could be tailored for each species to produce desired alveolar burdens of particles.

Predictable deposition, retention, and clearance patterns are possible for acute inhalation exposures of laboratory animal species and humans. Repeated exposures also occur for humans and are used routinely in laboratory animals to study the inhalation toxicology of a broad spectrum of potentially hazardous particulates. The predicted biokinetics of particles acutely inhaled can be readily extrapolated to repeated exposures. However, the predictions become increasingly questionable as exposure conditions deviate from those used for acute inhalation exposures. The following predictions for repeated inhalation exposures are therefore intended to be relative, rather than absolute, and were made using the assumption that physical clearance parameters for the A region are the same for acute and repeated inhalation exposures.

### 10.7.6.1 Human Estimates

The LUDEP® software version 1.1 for the 1994 ICRP66 model was also used to simulate chronic exposures of adult male "normal augmenters" to the trimodal aerosols described in Appendix 10C for Philadelphia (Figure 10C-2a, and Tables 10C-3 and 10C-4) and Phoenix (Figure 10C-2b, and Tables 10C-5 and 10C-6). The simulations were of a continuous 24 h/d and

7 d/week exposure at an air concentration of 50 $\mu g/m^3$. For both aerosols, the particles in the accumulation, intermediate, and coarse modes were assumed to have dissolution/absorption half times of 10, 100, and 1000 days, respectively.

Predicted particle mass ($\mu g$) lung burdens as a function of exposure days are presented in Figure 10-55a for the Philadelphia trimodal aerosol and in Figure 10-55b for the Phoenix trimodal aerosol. The assumed dissolution/absorption rates and default values for clearance parameters in the ICRP66 1994 model yielded predicted particle mass lung burdens from the accumulation, intermediate, and coarse modes that reached equilibrium between deposition and clearance after about 100, 700, and 7,000 days, respectively. Table 10-32 presents the predicted ratios of particle mass in the lungs for each of the three modes and for the total amount of particles. Individuals breathing the Phoenix aerosol would have about 0.7 the amount of the accumulation mode particles in the their lungs as would individuals breathing the Philadelphia aerosol, and about 1.5 times as much of the intermediate and 11 times as much of the coarse modes. Overall, individuals exposed for long periods to the Phoenix aerosol would have almost 4 times as much total mass of particles in their lungs as would individuals exposed to the Philadelphia aerosol. Interestingly, the biggest difference is in the predicted amounts of particles from the coarse mode.

Another way to present these model simulation results is to express them in terms of specific lung burden ($\mu g$ dust / g lung) versus time. This is presented in Figure 10-56a for the Philadelphia aerosol and in Figure 10-56b for the Phoenix aerosol. Note that the time of exposure was converted to age in years. Assuming that humans of all ages and gender deposit and clear about the same amounts of particles from these aerosols per day per gram of lung, this presentation of data approximates the specific lung burdens of particle mass as a function of age for young and old alike. For both aerosols, equilibrium amounts of dust are achieved after about 16-18 years. Assuming that clearance rates are not altered with age or these levels of particle burden, this suggests that an individual who has lived in these environments for longer than about 18 years has accumulated a specific lung burden of these particles and that the burdens will remain relatively constant as long as exposure conditions and health status are not appreciably changed. Note again that the data in Table 10-33 predict different relative amounts of accumulated particles from the three modes.

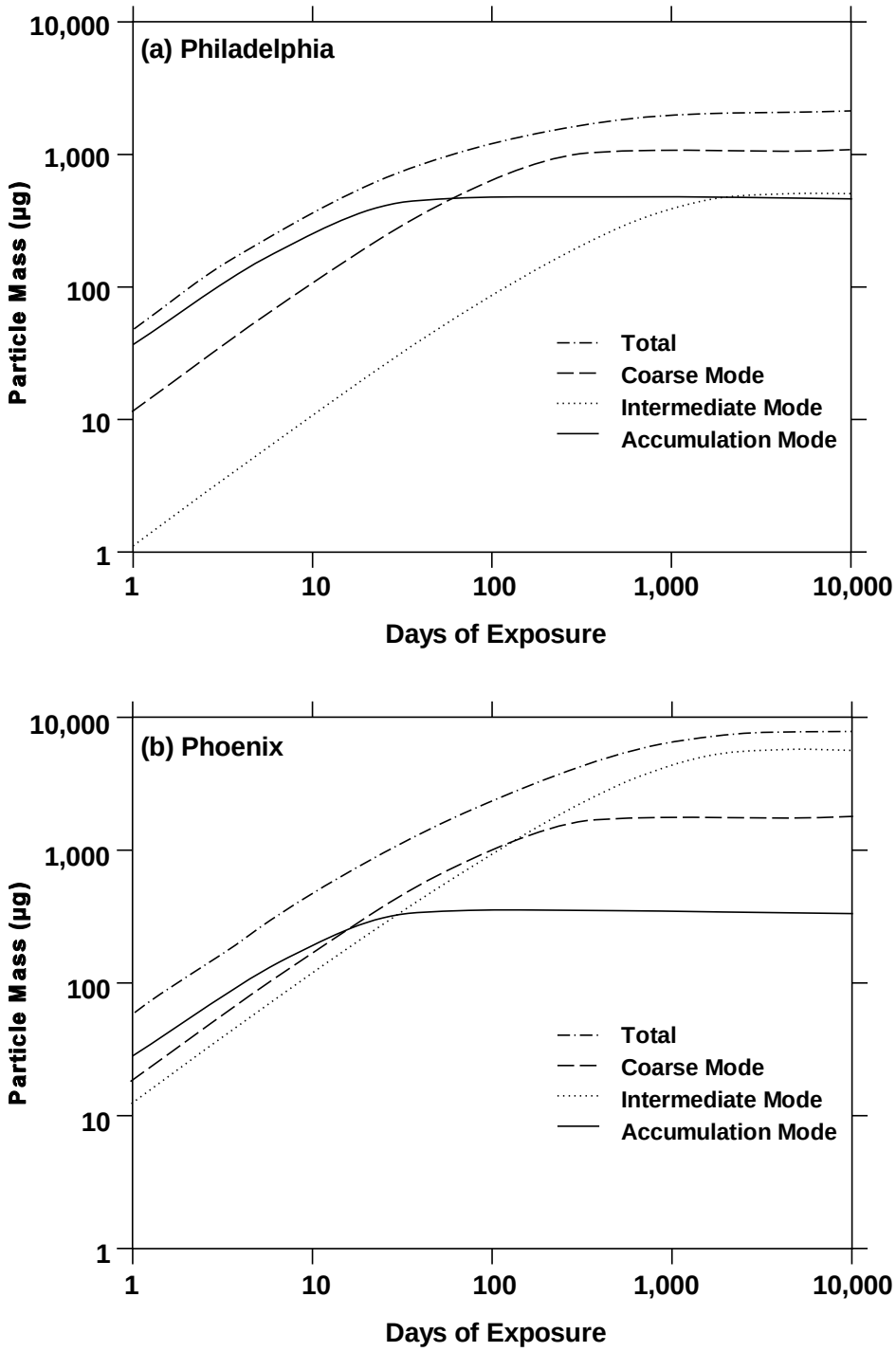


**Figure 10-55. Particle mass ($\mu$g) retained in the lung versus time (days of exposure) predicted by the International Commission on Radiological Protection Publication 66 (1994) model, assuming dissolution-absorption half-times of 10, 100, and 1,000 days for the accumulation, intermodal, and coarse modes, respectively, of continuous exposures to Philadelphia and Phoenix aerosols (described in Appendix 10C) at 50 $\mu$g/m$^3$. Predictions shown for a normal augmenter adult male with a general population activity level.**

## TABLE 10-32. PREDICTED RELATIVE PARTICLE MASS ($\mu$g) IN LUNGS OF ADULT MALE "NORMAL AUGMENTER" EXPOSED CHRONICALLY TO PHOENIX TRIMODAL AEROSOL VERSUS PHILADELPHIA TRIMODAL AEROSOL

| | Particle Mass ($\mu$g) Versus Mode: Ratio of Phoenix to Philadelphia Aerosols | | | |
|---|---|---|---|---|
| Day | Accum. | Intermed. | Coarse | Total |
| 1 | 0.71 | 1.52 | 10.8 | 1.14 |
| 2 | 0.71 | 1.52 | 10.8 | 1.14 |
| 4 | 0.71 | 1.52 | 10.8 | 1.16 |
| 6 | 0.71 | 1.52 | 10.8 | 1.18 |
| 8 | 0.71 | 1.52 | 10.8 | 1.20 |
| 10 | 0.71 | 1.52 | 10.8 | 1.23 |
| 12 | 0.72 | 1.52 | 10.8 | 1.25 |
| 14 | 0.72 | 1.52 | 10.8 | 1.27 |
| 16 | 0.72 | 1.52 | 10.8 | 1.29 |
| 18 | 0.72 | 1.52 | 10.8 | 1.31 |
| 20 | 0.72 | 1.52 | 10.8 | 1.32 |
| 25 | 0.72 | 1.52 | 10.8 | 1.37 |
| 30 | 0.72 | 1.52 | 10.8 | 1.42 |
| 40 | 0.72 | 1.52 | 10.8 | 1.50 |
| 60 | 0.72 | 1.52 | 10.8 | 1.64 |
| 80 | 0.72 | 1.52 | 10.8 | 1.75 |
| 100 | 0.72 | 1.52 | 10.8 | 1.84 |
| 150 | 0.72 | 1.52 | 10.8 | 2.01 |
| 200 | 0.72 | 1.52 | 10.8 | 2.15 |
| 250 | 0.72 | 1.52 | 10.8 | 2.26 |
| 300 | 0.72 | 1.52 | 10.8 | 2.36 |
| 400 | 0.72 | 1.52 | 10.8 | 2.55 |
| 500 | 0.72 | 1.53 | 10.8 | 2.70 |
| 600 | 0.72 | 1.53 | 10.8 | 2.83 |
| 700 | 0.72 | 1.53 | 10.8 | 2.94 |
| 800 | 0.72 | 1.53 | 10.8 | 3.04 |
| 900 | 0.72 | 1.53 | 10.8 | 3.12 |
| 1000 | 0.72 | 1.53 | 10.8 | 3.19 |
| 1200 | 0.72 | 1.53 | 10.8 | 3.28 |
| 1500 | 0.72 | 1.53 | 10.8 | 3.41 |
| 2000 | 0.72 | 1.53 | 10.8 | 3.51 |
| 2500 | 0.72 | 1.53 | 10.8 | 3.57 |
| 3000 | 0.72 | 1.53 | 10.8 | 3.60 |
| 3500 | 0.72 | 1.53 | 10.8 | 3.62 |
| 4000 | 0.72 | 1.53 | 10.8 | 3.63 |
| 4500 | 0.72 | 1.53 | 10.8 | 3.64 |
| 5000 | 0.72 | 1.53 | 10.8 | 3.64 |
| 5500 | 0.72 | 1.53 | 10.8 | 3.64 |
| 6000 | 0.72 | 1.53 | 10.8 | 3.64 |
| 7000 | 0.72 | 1.53 | 10.8 | 3.65 |
| 8000 | 0.72 | 1.53 | 10.8 | 3.65 |
| 9000 | 0.72 | 1.53 | 10.8 | 3.65 |
| 10,000 | 0.72 | 1.53 | 10.8 | 3.65 |

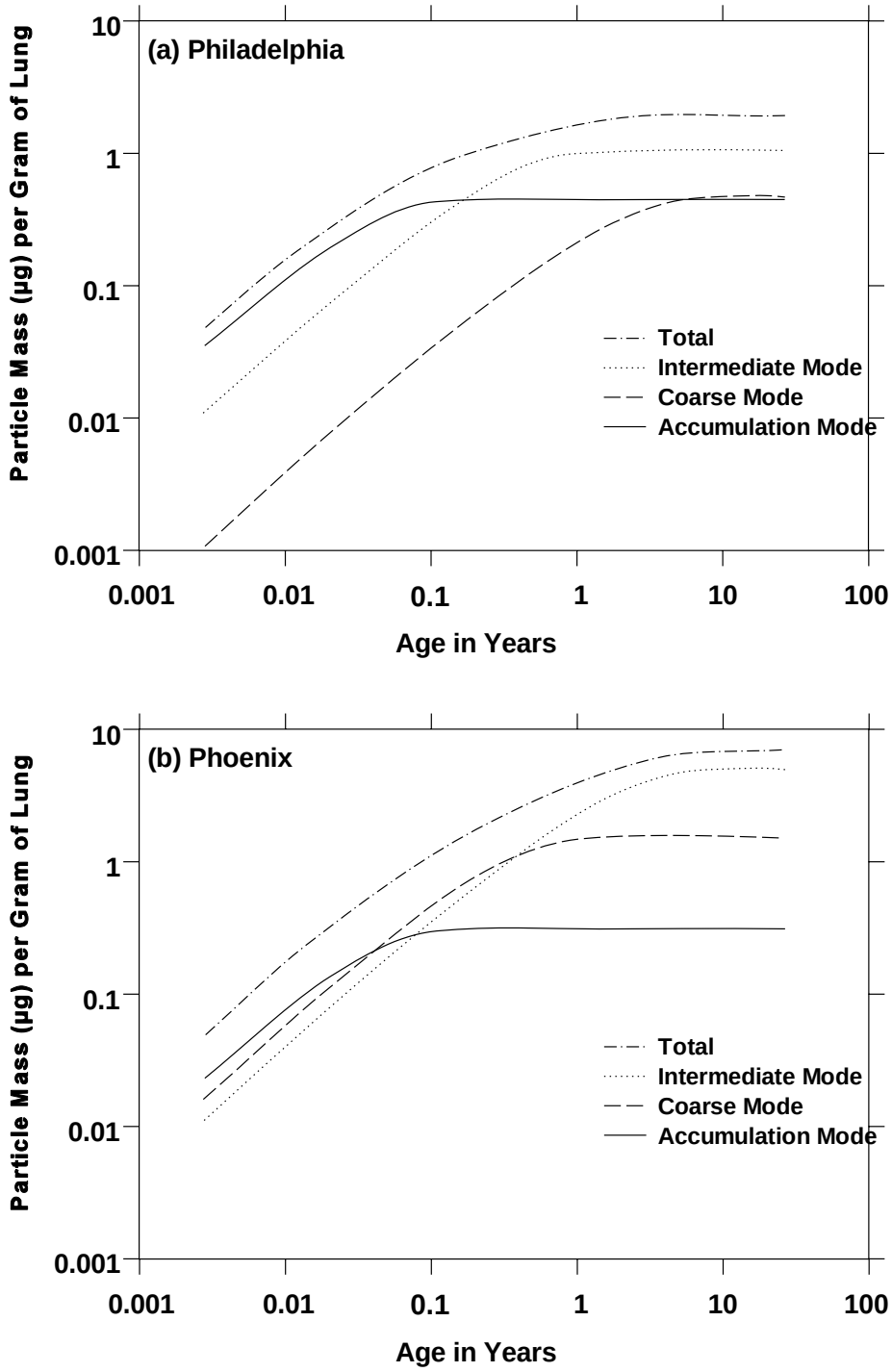


**Figure 10-56. Specific lung burden ($\mu$g particles/g lung) versus time (age in years) predicted by the International Commission on Radiological Protection Publication 66 (1994) model, assuming dissolution-absorption half-times of 10, 100, and 1,000 days for the accumulation, intermodal, and coarse modes, respectively, of continuous exposures to Philadelphia and Phoenix aerosols (described in Appendix 10C) at 50 $\mu$g/m$^3$. Predictions shown for a normal augmenter adult male with a general population activity level.**

### 10.7.6.2 Laboratory Animal Estimates

Deposition data for two different aerosols, one with an MMAD of 1.0 and $\sigma_g$ of 1.3, the other with an MMAD of 2.55 and a $\sigma_g$ = 2.4 were chosen to calculate total alveolar retention (Table 10-33). The aerosol with an MMAD of 1.0 $\mu$m and $\sigma_g$ of 1.3 was chosen as the smallest particle diameter for which the laboratory animal dosimetry model calculates fractional deposition and to represent a relatively monodisperse distribution. The aerosol with an MMAD of 2.55 $\mu$m and a $\sigma_g$ of 2.4 was chosen to approximate a hypothetical $PM_{10}$ aerosol in which the $PM_{2.5}$ to $PM_{10}$ sample size cut ratio is 0.6 Dockery and Pope (1994).

**TABLE 10-33. FRACTION OF INHALED PARTICLES DEPOSITED IN THE ALVEOLAR REGION OF THE RESPIRATORY TRACT FOR RATS AND ADULT MALE HUMANS**

| | Fraction of Aerosol Deposited in Alveolar Region | |
|---|---|---|
| Aerosol Parameters | Rat[a] | Human[b] |
| 1.0 $\mu$m MMAD, $\sigma_g$ = 1.3 | 0.063 | 0.119 |
| 2.55 $\mu$m MMAD, $\sigma_g$ = 2.4 | 0.031 | 0.102 |

[a]From Tables 10-30 and 10-31.
[b]From (ICRP 66, 1994) average for general population activity pattern (8 h sleeping, 8 h sitting, and 8 h light activity) for adult male "normal augmenter" (See Table 10-18).

Table 10-34 provides fractional deposition data in the alveolar region for three different aerosols as predicted for the various demograhic groups. Table 10-35 provides the particle deposition rates ($\mu$g/d) in the alveolar regional for a 24-h exposure to an airborne mass concentration of 50 $\mu g/m^3$. Although model simulations of retained particle burdens were not performed for these various cohorts, differences in retained particle burdens can be expected because the clearance modeling output is proportional to the deposition fractions used as input. Note the greater deposition efficiency for the larger diameter aerosols in elderly males and in those with respiratory disease.

Table 10-36 summarizes the common and specific parameters used for predicting alveolar burdens for exposures of humans and rats of the two different aerosols at a concentration of 50 µg particles/$m^3$. Exposures were assumed to take place 24 h/day at the

**TABLE 10-34. FRACTION OF INHALED PARTICLES DEPOSITED IN THE ALVEOLAR REGION OF THE RESPIRATORY TRACT FOR DIFFERENT DEMOGRAPHIC GROUPS**

| | Fraction of Aerosol Deposited in Alveolar Region[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| Aerosol Parameters | Male Worker (18-44)[b] | Female Worker (18-44) or Elderly Female (over 65)[c] | Elderly Male over 65[d] | Male Respiratory Compromised[e] | Child (14-18)[f] | Child (6-13)[g] | Child (0-5)[h] |
| 0.5 $\mu$m MMAD, $\sigma_g$ = 1.3 | 0.085 | 0.079 | 0.085 | 0.086 | 0.079 | 0.067 | 0.069 |
| 1.0 $\mu$m MMAD, $\sigma_g$ = 1.3 | 0.135 | 0.125 | 0.138 | 0.139 | 0.120 | 0.098 | 0.094 |
| 2.55 $\mu$m MMAD, $\sigma_g$ = 2.4 | 0.118 | 0.108 | 0.123 | 0.126 | 0.091 | 0.073 | 0.062 |

[a]Calculated using ICRP Publication 66 lung deposition model with EPA's hourly lung ventilation rates for each demographic group.
[b]Total daily volume of air breathed by a male worker is 19.4 $m^3$.
[c]Total daily volume of air breathed by a female worker is 16.5 $m^3$, and 16.1 $m^3$ for a female over age 65.
[d]Total daily volume of air breathed by a male over 65 years old is 18.1 $m^3$.
[e]Total daily volume of air breathed by a an adult male with compromised respiratory system is 17.4 $m^3$.
[f]Total daily volume of air breathed by a a child of age 14-18 years is 25.5 $m^3$.
[g]Total daily volume of air breathed by a a child of age 6-13 years is 18.2 $m^3$.
[h]Total daily volume of air breathed by a a child of age 0-5 years is 11.6 $m^3$.



**TABLE 10-35. PARTICLE DEPOSITION RATES ($\mu$g/d) IN THE ALVEOLAR REGION (FOR 24-H EXPOSURE TO AN AIRBORNE MASS CONCENTRATION OF 50 $\mu g/m^3$)**

| | Daily Mass Deposition in Alveolar Region | | | | | | |
|---|---|---|---|---|---|---|---|
| Aerosol Parameters | Male Worker (18-44) | Female Worker (18-44) | Male over 65 | Male Respiratory Compromised | Child (14-18) | Child (6-13) | Child (0-5) |
| 0.5 $\mu$m MMAD, $\sigma_g$ = 1.3 | 82.5 | 65.2 | 76.9 | 74.8 | 100.7 | 61.0 | 40.0 |
| 1.0 $\mu$m MMAD, $\sigma_g$ = 1.3 | 131.3 | 102.8 | 124.7 | 121.2 | 153.0 | 88.7 | 54.6 |
| 2.55 $\mu$m MMAD, $\sigma_g$ = 2.4 | 114.5 | 89.1 | 111.3 | 109.6 | 116.0 | 66.4 | 36.0 |

**TABLE 10-36. SUMMARY OF COMMON AND SPECIFIC INHALATION EXPOSURE PARAMETERS USED FOR PREDICTING ALVEOLAR BURDENS OF PARTICLES INHALED BY RATS AND HUMANS**

A. Common Parameters:

| | |
|---|---|
| Exposure atmosphere | 50 µg/m$^3$ |
| Particle MMAD, $\sigma_g$ | 1.0 $\mu$m, 1.3; or 2.55 $\mu$m, 2.4 |
| Particle dissolution-absorption half-time | 10, 100, or 1,000 days |
| Chronic inhalation exposure pattern | 24 h/day; 7 days/week |
| Duration of continuous exposure | 2 years |

B. Specific Parameters: Particle deposition rates in the alveolar region; data calculated using information in Tables 10-33 and Appendix 10B, Tables 10B-1 and 10B-2

| Species | Daily Deposition of 1.0 $\mu$m MMAD, $\sigma_g$ = 1.3 | | Daily Deposition of 2.55 $\mu$m MMAD, $\sigma_g$ = 2.4 | |
|---|---|---|---|---|
| | $\mu$g | $\mu$g/g lung | $\mu$g | $\mu$g/g lung |
| Rat | 1.14 | 0.26 | 0.56 | 0.13 |
| Human[a] | 118 | 0.11 | 101 | 0.092 |

[a]Based on human deposition parameters from ICRP66 (ICRP, 1994) for an average general population activity pattern (8 h sleeping, 8 h sitting, and 8 h light activity) for adult male "normal augmenter" (See Table 10B-1 in Appendix 10B).

average minute respiratory ventilation and deposition fractions presented in Tables 10B-1, 10B-2, and 10-34. Daily alveolar deposition was expressed in units of $\mu$g particles/g lung to normalize deposition rates between the two species. Particle dissolution-absorption rates were varied; half-times of 10, 100, and 1000 days were used to simulate particles that are relatively soluble, moderately soluble, and poorly soluble. The A clearance parameters in Table 10-16 derived from the results of acute inhalation exposures of laboratory animals, were used to predict the consequences of repeated exposures of these animals. For human modeling of acute or repeated inhalation exposures, the clearance parameters as recommended by the ICRP (ICRP66, 1994) were used in the human model LUDEP® version 1.1 software.

Table 10-37 shows the calculated alveolar particle burdens of the 1.0 $\mu$m MMAD ($\sigma_g$ = 1.3) aerosol in rats and an adult human normal augmenter for a general population activity pattern, assuming a particle dissolution-absorption half-time of 10, 100, and 1,000 days, respectively. Table 10-38 shows the analogous calculated alveolar particle

## TABLE 10-37. ALVEOLAR PARTICLE BURDENS ($\mu$g) OF EXPOSURE TO 50 $\mu g/m^3$ OF 1.0 $\mu$m MASS MEDIAN AERODYNAMIC DIAMETER (MMAD) AEROSOL, ASSUMING PARTICLE DISSOLUTION-ABSORPTION HALF-TIME OF 10, 100, OR 1,000 DAYS

| | 10 Days | | 100 Days | | 1000 Days | |
|---|---|---|---|---|---|---|
| Exposure Days | Rat | Human | Rat | Human | Rat | Human |
| 1 | 1.04 | 114 | 1.11 | 117 | 1.11 | 117 |
| 7 | 5.52 | 642 | 6.96 | 790 | 7.13 | 808 |
| 14 | 8.31 | 1020 | 12.4 | 1510 | 13.0 | 1580 |
| 21 | 9.74 | 1250 | 16.8 | 2170 | 17.8 | 2310 |
| 28 | 10.5 | 1380 | 20.2 | 2780 | 21.9 | 3020 |
| 35 | 10.9 | 1460 | 23.1 | 3340 | 25.3 | 3700 |
| 50 | 11.2 | 1540 | 27.5 | 4400 | 31.2 | 5090 |
| 75 | 11.3 | 1570 | 32.1 | 5840 | 37.9 | 7210 |
| 91 | 11.3 | 1580 | 33.9 | 6600 | 40.9 | 8460 |
| 100 | 11.3 | 1580 | 34.7 | 6980 | 42.4 | 9160 |
| 150 | 11.3 | 1580 | 37.4 | 8610 | 48.1 | 12700 |
| 200 | 11.3 | 1580 | 38.6 | 9690 | 51.8 | 15900 |
| 300 | 11.3 | 1580 | 39.7 | 10900 | 56.6 | 21600 |
| 400 | 11.3 | 1580 | 40.1 | 11500 | 59.8 | 26400 |
| 500 | 11.3 | 1580 | 40.2 | 11700 | 62.1 | 30500 |
| 600 | 11.3 | 1580 | 40.3 | 11800 | 63.9 | 34100 |
| 700 | 11.3 | 1580 | 40.3 | 11900 | 65.3 | 37100 |
| 730 | 11.3 | 1580 | 40.3 | 11900 | 65.7 | 38000 |

**TABLE 10-38. ALVEOLAR PARTICLE BURDENS ($\mu$g) OF EXPOSURE TO 50 $\mu g/m^3$ OF 2.55 $\mu$m MASS MEDIAN AERODYNAMIC DIAMETER (MMAD) AEROSOL, ASSUMING PARTICLE DISSOLUTION-ABSORPTION HALF-TIME OF 10, 100, OR 1,000 DAYS**

| | 10 Days | | 100 Days | | 1000 Days | |
|---|---|---|---|---|---|---|
| Exposure Days | Rat | Human | Rat | Human | Rat | Human |
| 1 | 0.51 | 96.0 | 0.54 | 99.1 | 0.54 | 99.3 |
| 7 | 2.70 | 542 | 3.40 | 666 | 3.49 | 681 |
| 14 | 4.06 | 861 | 6.07 | 1280 | 6.34 | 1330 |
| 21 | 4.76 | 1050 | 8.19 | 1830 | 8.71 | 1950 |
| 28 | 5.12 | 1160 | 9.89 | 2340 | 10.7 | 2540 |
| 35 | 5.31 | 1230 | 11.3 | 2820 | 12.4 | 3120 |
| 50 | 5.47 | 1300 | 13.5 | 3710 | 15.2 | 4290 |
| 75 | 5.53 | 1320 | 15.7 | 4930 | 18.5 | 6080 |
| 91 | 5.53 | 1330 | 16.6 | 5570 | 20.0 | 7140 |
| 100 | 5.53 | 1330 | 17.0 | 5890 | 20.7 | 7730 |
| 150 | 5.53 | 1330 | 18.3 | 7260 | 23.5 | 10700 |
| 200 | 5.53 | 1330 | 18.9 | 8170 | 25.3 | 13400 |
| 300 | 5.53 | 1330 | 19.4 | 9200 | 27.7 | 18200 |
| 400 | 5.53 | 1330 | 19.6 | 9660 | 29.2 | 22200 |
| 500 | 5.53 | 1330 | 19.6 | 9890 | 30.4 | 25800 |
| 600 | 5.53 | 1330 | 19.7 | 9980 | 31.2 | 28700 |
| 700 | 5.53 | 1330 | 19.7 | 10000 | 31.9 | 31300 |
| 730 | 5.53 | 1330 | 19.7 | 10000 | 32.1 | 32000 |

burdens for the 2.55 $\mu$m MMAD ($\sigma_g$ = 2.4) aerosol. Note the different patterns for accumulations of A burdens of particles for these species. These simulations suggest that significant A burdens of particles can be reached with exposures to relatively low aerosol concentrations of 50 $\mu g/m^3$. Particle burdens increase with time until an equilibrium burden is achieved. This burden is achieved more rapidly for less soluble particles. The maximal equilibrium particle burden is much higher for poorly soluble particles and also slightly higher for the smaller diameter (1 $\mu$m) particles.

The exposure concentration is representative of environmental ambient aerosols that have been recorded for numerous American and European cities. An important point to make is that the composition of the ambient aerosols vary from one place to another and constituents of the aerosols undoubtedly cover a broad range of solubilization and absorption characteristics. Therefore, the composition of the retained particles would be expected to change with time and the accumulated A burdens would consist of the more persistent types of particles or constituents of particles present in ambient aerosols. The more soluble, and perhaps more toxic, constituents of the aerosols will be rapidly absorbed into the circulatory system, metabolized, excreted, or redeposited in body organs.

Data in Tables 10-37 and 10-38 were used together with the data in Table 10B-2 to calculate the $\mu$g of particles per gram of lung tissue for each aerosol at each of the assumed particle dissolution-absorption half-life times. Panels a, b, and c in Figure 10-57 show the alveolar particle burdens normalized to lung tissue weight ($\mu$g particles per g lung tissue) for the 1.0 $\mu$m MMAD ($\sigma_g$ = 1.3) aerosol assuming particle dissolution-absorption half-times of 10, 100, and 1,000 days, respectively. Panels a, b, and c in Figure 10-58 show the alveolar particle burdens normalized to lung tissue weight ($\mu$g particles per g lung tissue) for the 2.55 $\mu$m MMAD ($\sigma_g$ = 2.4) aerosol assuming particle dissolution-absorption half-times of 10, 100, and 1,000 days, respectively. The rat alveolar burden is predicted to be greater than that of humans if a dissolution-absorption half-time of 10 days is assumed but remains at lower alveolar particle burdens than the humans if 100 or 1,000 days is assumed for the dissolution-absorption half-time.

Figure 10-58 shows the rat and human alveolar particle burdens for the larger diameter and more polydisperse aerosol (2.55 $\mu$m MMAD, $\sigma_g$ = 2.4). At short dissolution-absorption half-times, the rat and human are predicted to have very similar alveolar particle burdens,

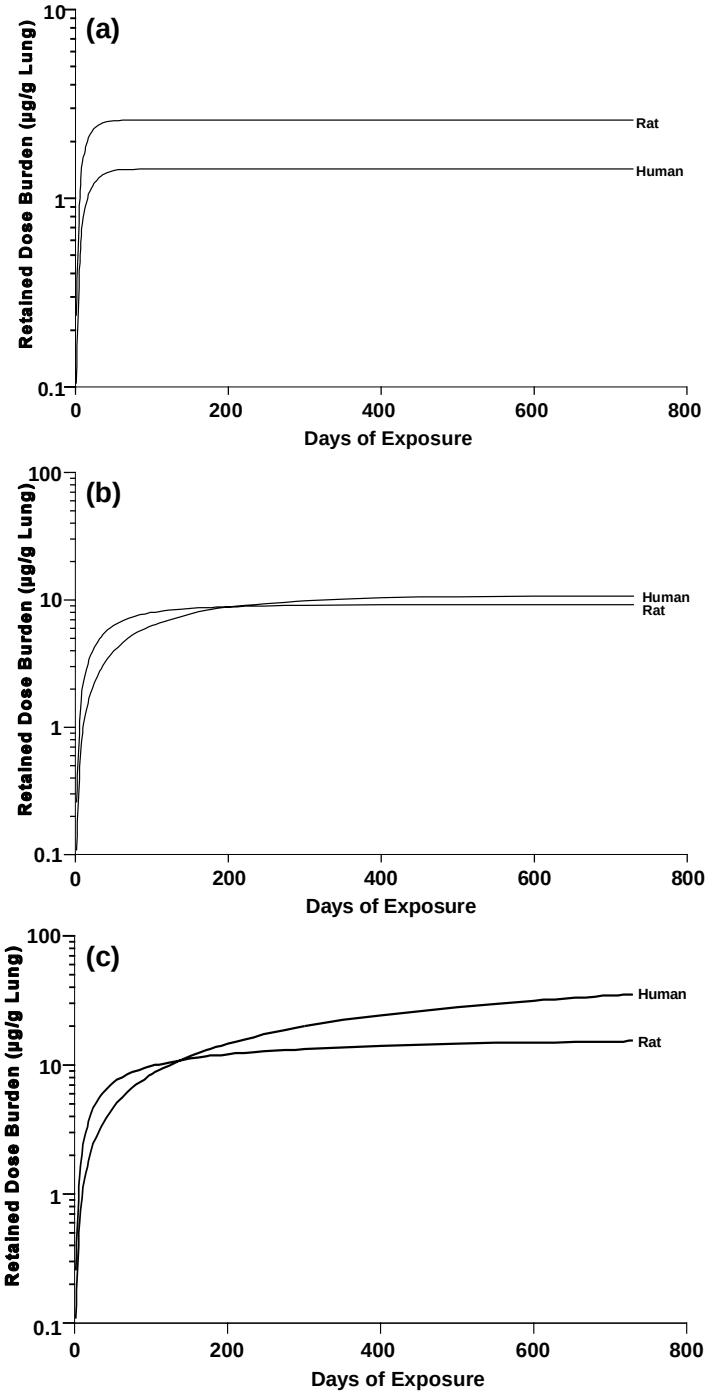


**Figure 10-57. Predicted retained alveolar dose ($\mu$g/g lung) in a normal augmenter human or in a rat for exposure at 50 $\mu$g/m$^3$ to 1.0 $\mu$m mass median aerodynamic diameter (MMAD) monodisperse ($\sigma_g$ = 1.3) aerosol, assuming a dissolution-absorption half-time of (a) 10 days, (b) 100 days, or (c) 1,000 days.**

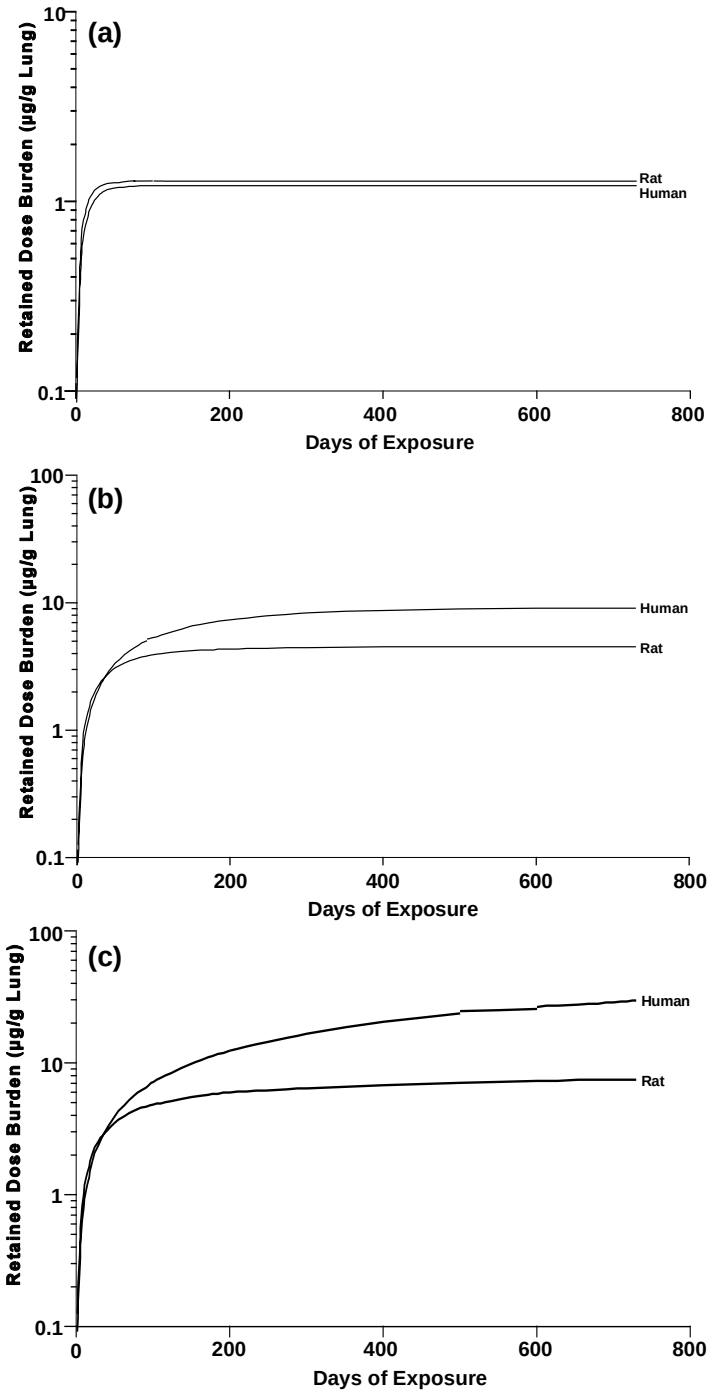


**Figure 10-58. Predicted retained alveolar dose ($\mu$g/g lung) in a normal augmenter human or in a rat for exposure at 50 $\mu$g/m$^3$ to 2.55 $\mu$m mass median aerodynamic diameter (MMAD) polydisperse aerosol ($\sigma_g$ = 2.4), assuming a dissolution-absorption half-time (a) of 10 days, (b) 100 days, or (c) 1,000 days.**

with the rat having a slightly greater burden at an assumed dissolution-absorpton half-time of 10-days. At an assumed dissolution-absorption half-time of 100 days, rat alveolar particle burden less than that of humans. By 1000 days, the rat burden is considerably lower.

Panels (a) through (c) in Figure 10-59 show the rat to human alveolar retained dose ratios ($\mu$g/d lung) for both aerosols and assuming particle dissolution-absorption half-times of 10, 100, and 1,000 days, respectively. Because retention involves clearance processes that can translocate particle mass, the particle mass burden was normalized to lung tissue weight ($\mu$g particles per g lung tissue). These ratios could be calculated using Equation 10-54 and could be used for interspecies extrapolation of "chronic" effects. Tables 10-38 and 10-39 provide the ($AI_t$) term. Tables 10-27 through 10-32 provide the ($F_{r_A}$) term. Normalizing factor data and ventilation rates for laboratory humans and laboratory animals are provided in Tables 10B-1 and 10B-2, respectively. These figures present the $RRDR_{A[ACT]}$ values that would be applied to a given concentration to calculate an HEC for the rat for these simulated continuous exposures. It is apparent that a substantial range of exposure concentrations would be required to produce the same specific A burdens in these mammalian species, and the exposure concentrations depend on the exposure protocol, or study duration. These results demonstrate the importance of understanding respiratory, deposition, and physical clearance parameters of humans and laboratory animals, as well as the dissolution-absorption characteristics of the inhaled particles. This combination of factors results in significant species differences in A accumulation patterns of inhaled particles during the course of repeated or chronic exposures which must be considered in experiments designed to achieve equivalent alveolar burdens, or in evaluating the results of inhalation exposures of different mammalian species to the same aerosolized test materials.

These retained dose ratios are different than those predicted for deposited dose, reflecting both a difference in normalizing factor as well as differences in clearance rates and the dissolution-absorption characteristics of the inhaled particles.

### 10.7.7 Summary

Major factors that affect the disposition (deposition, uptake, distribution, metabolism, and elimination) of inhaled particles in the respiratory tract include physicochemical characteristics of the inhaled aerosol (e.g., particle size, distribution, solubility,

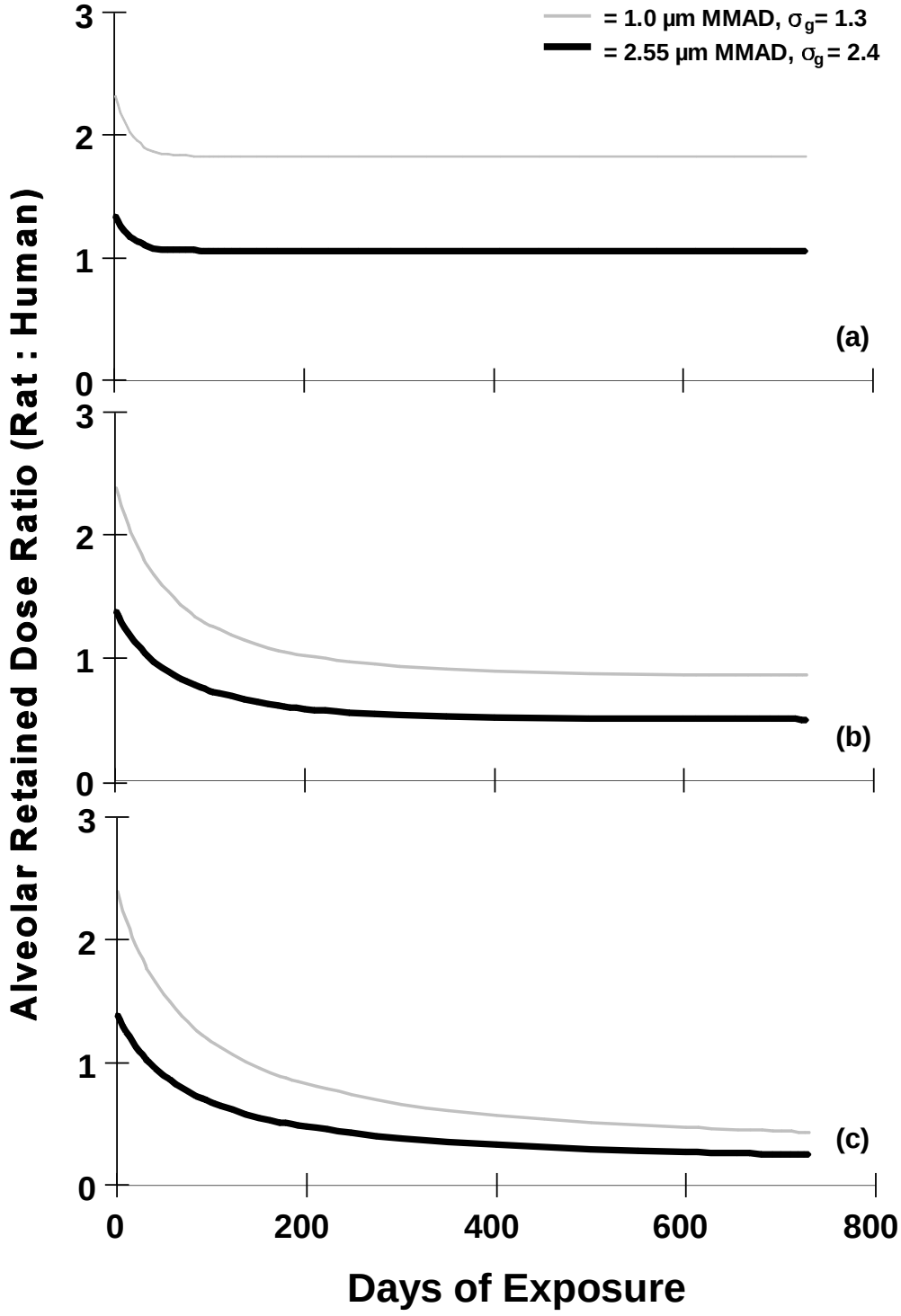


**Figure 10-59. Predicted alveolar region retained dose ratios in rats versus humans for chronically inhaled exposure at 50 $\mu$g/m$^3$ to 1.0 $\mu$m mass median aerodynamic diameter (MMAD) monodisperse ($\sigma_g$ = 1.3) and 2.55 $\mu$m MMAD polydisperse ($\sigma_g$ = 2.4) aerosols, assuming a dissolution- absorption half-time of (a) 10 days, (b) 100 days, or (c) 1,000 days.**

hygroscopicity) and anatomic (e.g., architecture and size of upper and lower airways, airway diameters, airway lengths, branching patterns) and physiological (e.g., ventilation rates, clearance mechanisms) parameters of individual mammalian species.

Differences in susceptibility can be due to either differences in dosimetry (i.e., differences in deposited and retained particle mass or number) or tissue sensitivity. The simulations performed herein were limited to an exploration of differences in dosimetry. At present, respiratory tract dosimetry must rely on many simplifications and empiricisms, but even a somewhat rudimentary effort assists in linking exposure to potential effects, provides insight on intrahuman variability, and aids interspecies extrapolations.

The objective of this exercise was to provide useful insights about dose metrics such as average mass concentrations and average numbers of particles per unit area of respiratory regions. Construction of more detailed theoretical or PBPK model structures to explore site-specific dosimetry at the level of individual lung lobes awaits the availability of data with which to estimate parameters.

Dose may be accurately described by particle deposition alone if the particles exert their primary action on the surface contacted (Dahl et al., 1991), i.e., deposited dose may be an appropriate metric for acute effects. For longer-term effects, the initially deposited dose may not be as decisive a metric since particles clear at varying rates from different lung regions. To characterize these effects, a retained dose that includes the effects of both deposition and clearance is more appropriate. For the present document, average deposited particle mass burden in each region of the respiratory tract was selected as the dose metric for "acute" effects in both humans and laboratory animals. Average retained particle mass burden in each region for humans and in the lower respiratory tract for laboratory animals was selected as the dose metric for "chronic" effects. These choices were dictated by the availability of the dosimetry models and the input of anatomical and morphometric information.

Ventilatory activity pattern and breathing mode (nose or mouth) were confirmed as major factors affecting inhaled particle deposition. Variations in mass deposition fraction were shown for adult males with a general population activity pattern versus adult male workers with light or heavy activity patterns. Eight demographic groups were constructed that differed in ventilation pattern by age, gender, and cardiopulmonary health status. In the alveolar (A) region, the cohort of children 14 to 18 years showed slightly higher deposition of particles less than approximately

0.1 $\mu$m when compared to the other cohorts, whereas the cohort of children 0 to 5 years showed a decrease. When evaluated on the basis of daily mass deposition ($\mu$g/d), the cohort of children ages 14 to 18 years showed an increase in deposition for all three regions of the respiratory tract compared to other cohorts, whereas the cohort of children 0 to 5 years showed a decrease. This is due primarily to differences in minute volume relative to lung size.

Other differences in dosimetry such as altered respiratory tract architecture with altered flow pattern or differences in susceptibility of the target tissue are not addressed in these simulations. As discussed earlier, Anderson et al. (1990) have shown enhanced deposition of ultrafine particles in patients with COPD compared to healthy subjects. Miller et al. (1995) used a more detailed theoretical multipath model and estimated enhanced deposition in a model of compromised lung status defined by decreased ventilation to some parts of the respiratory tract. The simulations performed herein were limited to average particle mass burdens in each region of the respiratory tract. Nevertheless, these simulations do suggest differences for these cohorts. For example, the cohort of children 14 to 18 years showed an enhanced deposition rate (ug/d) for submicron-sized particles in all three respiratory tract regions whereas children 0 to 5 years showed a decrease deposition rate relative to male and female adults. For larger particles (micron-sized and above), the 14 to 18-year cohort showed no enhanced deposition rate in the tracheobronchial or alveolar regions compared to adults, and younger children cohorts showed a progressive decrease with decreasing age.

A number of simulations were performed in order to illustrate the relationship between deposition efficiency of the respiratory tract, mass burden of particles in the thoracic portion of the respiratory tract, and the mass distribution of aerosols collected by a PM10 or $PM_{2.5}$ sampler. Simulations were performed for single mode aerosols of different particle diameters. It is clear that mouth (habitually oronasal) breathers have a greater deposition of particles >1 μm than do normal augmenter (habitually nasal) breathers. Whereas $PM_{10}$ accounts for all particles in the thoracic size deposition mode, the $PM_{2.5}$ sample does not include some larger particles that would be deposited in the TB and A regions of mouth breathers, under the simulated conditions (general population activity pattern 8 h sleep, 8 h sitting, 8 h light activity). Habitual oronasal (mouth) breathers do not represent a large percentage of the population, but are cited here to illustrate the difference effect of breathing habit.

Because the real world situation is more complex and ambient aerosols are multi-modal having a broad distribution of particle size and composition, similar simulations were performed using ambient aerosols, as characterized for either Philadelphia or Phoenix. These simulations of ambient aerosols showed that the $PM_{2.5}$ sampler distribution accounts for the particle mass in the fine (<1.0 μm) mode and the transition mode (MMAD ~2.5 μm) but does not account for the smaller mass of coarse mode particles that would be deposited in the thorax (mainly affecting tracheobronchial deposition in mouth breathers). Failure of $PM_{2.5}$ to account for coarse mode particle thoracic deposition is more severe for the Phoenix aerosol than for the Philadelphia aerosol.

Doses are conventionally expressed in terms of particle mass (gravimetric dose). However, when different types of particles are compared, doses may be more appropriately expressed as particle volume, particle surface area, or numbers of particles, depending on the effect in question (Oberdörster et al., 1994). For example, the retardation of alveolar macrophage-mediated clearance due to particle overload appears to be better correlated with phagocytized particle volume rather than mass (Morrow, 1988). The smaller size fractions of aerosols are associated with the bulk of surface area and particle number. That is, concentrations in this size fraction are very small by mass but extremely high by number. The need to consider alternative dose metrics such as number is accentuated when the high rate of deposition of small particles in the lower respiratory tract (TB and A regions), the putative target for the mortality and morbidity effects of PM exposures, is also taken into account. Simulations of particle number deposition fraction for ambient aerosols characterized for Philadelphia and Phoenix confirm that the fine mode contributes the highest deposition fraction in each region of the respiratory tract. Particle numbers deposited per day were shown to be on the order of 100,000,000 and 1,000,000,000 for the fine mode of Philadelphia and Phoenix, respectively, for hypothethical exposure to a total aerosol mass concentration of 50 $\mu g/m^3$.

Inhalability is a major factor influencing interspecies variability. At the larger particle diameters (MMAD > 2.5 $\mu$m for $_g$ = 1.3), the laboratory animal species have very little lower respiratory tract deposition due to the low inhalability of these particles. This may help explain why inhalation exposures of laboratory animals to high concentrations of larger diameter particles have exhibited little effect in some bioassays.

Simulations of retained particle burdens confirmed solubility as a major factor influencing clearance. Assumptions with respect to dissolution-halftimes (10, 100, or 1,000 days) were shown to dramatically influence the predicted particle mass burdens. Data on in vivo solubility are needed to enhance modeling of clearance in all species. Retained particle burden accumulates more rapidly and reaches a higher equilibrium burden when the particles are poorly soluble.